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Two prospective studies found that elevated 2-hr glucose predicted male mortality independent of fasting glucose and HbA1c

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Abstract

Objective: To quantify the relative contribution of elevated 2-hr glucose, fasting glucose (FPG), and HbA1c to all-cause mortality.

Study Design and Setting: A joint analysis of two prospective studies with baseline glycemia measurements.

Results: The multivariate adjusted hazard ratios (HRs) corresponding to a one standard deviation increase in HbA1c were 1.14 (95% CI 1.03–1.25), 1.08 (0.98–1.19) for FPG and 1.15 (1.05–1.27) for 2-hr glucose, respectively. Entering the 2-hr glucose to the model based on the FPG and HbA1c significantly improved the prediction of mortality, whereas neither FPG, nor HbA1c added significant information once 2-hr glucose was in the models. In subjects with FPG $<$7.0 mmol/L and HbA1c $\leq$6.5%, the HR was 1.35 (1.03–1.78) in men with 2-hr glucose $\geq$7.8 mmol/L compared with men with 2-hr glucose $<$7.8 mmol/L.

Conclusion: Elevated 2-hr glucose was a predictor of mortality independent of the levels of fasting glucose and HbA1c.

Keywords: HbA1c; 2-Hour glucose; Fasting glucose; All-cause mortality

1. Introduction

Recent studies have shown that 2-hr glucose is an independent risk factor for all-cause and cardiovascular mortality in subjects not previously diagnosed as diabetic and a better predictor of mortality than fasting glucose (FPG) [1–7]. The DECODE (*D*iabetes *E*pidemiology: *C*ollaborative analysis *O*f *D*iagnostic criteria in *E*urope) Study [1–3] revealed that mortality increased with increasing 2-hr glucose concentration after a 75-g oral glucose load within any category of fasting glucose, and that the largest absolute number of excess deaths were attributed to impaired glucose tolerance. In contrast, such trend with increasing fasting glucose levels for the 2-hr glucose categories was not found. Postprandial hyperglycemia, but not fasting hyperglycemia, was an independent risk factor for myocardial infarction and total mortality in the Diabetes Intervention Study [4]. Isolated postchallenge hyperglycemia, that is, asymptomatic diabetes identified by the 2-hr glucose alone, has been found to double the mortality risk in middle-aged populations [5] and as well as in older women [6]. Postprandial plasma glucose level, but not fasting glucose level was independently associated with an increased carotid intima-media thickness [7]. More recently, the data analysis based on the five Finnish DECODE cohorts showed that in subjects without a prior history of diabetes the association of 2-hr glucose with serious coronary heart disease (CHD) incidence (CHD death and nonfatal myocardial infarction) is graded and independent, and that 2-hr glucose is superior to fasting glucose in assessing the risk of future CHD events [8]. These studies, however, did not account for HbA1c, which is an indicator for the average level of glycemia over several months. The predictive value of HbA1c for mortality in the general population is less known. In one prospective study [9], HbA1 but not 2-hr or fasting glucose was related to cardiovascular mortality but not to all-cause mortality in women only. In contrast, 2-hr glucose was shown to be a better predictor for all-cause mortality than FPG or HbA1c in the Hoorn study [10], as well as in the Framingham Offspring study [11]. Also, Khaw et al. [12] reported that HbA1c was continuously related to subsequent

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mortality from all-cause, cardiovascular, and ischemic heart disease across the whole population distribution of HbA1c, with the lowest rates in people whose HbA1c concentration was below 5%. However, data on FPG or 2-hr glucose was not available in this latter study. In the present study, data from two DECODE cohorts were analyzed to quantify simultaneously the relative contribution of fasting, 2-hr glucose, and HbA1c to all-cause mortality in men.

2. Subjects and methods

2.1. Subjects and cohorts

Two population-based studies that have been included in the DECODE study contributed their data to this joint analysis. The Hoorn Study is a cohort study of glucose intolerance in a Dutch population aged 49–77 years, which started in 1989 [10,13,14]. The Finnish cohort was first examined in 1959 in connection with the Seven Countries Study [15–17], and the glucose tolerance test was administrated to the survivors of the cohort in 1989 when the population was 70–89 years old [18,19]. Subjects with insulin or oral hypoglycemic medication at baseline were classified as previously diagnosed diabetic and excluded from the current data analysis. Men not previously diagnosed as diabetic and having baseline glycemic measurements on HbA1c and on plasma glucose at fasting and 2-hr after a 75-g oral glucose tolerance test and having all other risk factors required for the analysis were included in the data analysis. A total of 1,097 men were from the Hoorn Study and 314 men from the Finnish cohort. Vital status was collected for all subjects from the population register of the city of Hoorn as of the end of 1999 in the Hoorn cohort and from the National Death Register as of the end of 1997 in the Finnish cohort. The median follow-up was 8.8 years for the Hoorn cohort and 8.1 years for the Finnish cohort, and a total of 11,005 person-years were accumulated.

The cohorts and the baseline measurements have been described in detail previously [10,13–19]. Briefly, a fasting blood sample was taken from all participants after overnight fasting, and then, an oral 75-g glucose load was given. Fasting and 2-hr postload plasma glucose concentrations were determined with a glucose dehydrogenase method in the both cohorts. HbA1c was determined by ion-exchange high-performance liquid chromatography in both cohorts at the time of the baseline surveys. Fasting insulin was determined using a specific double-antibody radioimmuno assay (Linco, St. Louis, MO) in the Hoorn Study and Phadeseph Insulin RIA100 (Pharmacia Diagnostics AB, Uppsala, Sweden) in the Finnish cohort. In both cohorts, cardiovascular risk factors, including total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure, height, and weight were also determined. Body mass index (BMI) was calculated by dividing the weight (kg) by height (m) squared. Smoking status was classified as nonsmokers, ex-smokers, and current smokers.

2.2. Statistical analysis

HbA1c concentration was classified into quintiles, and the baseline risk factors were computed for the five categories of HbA1c (Tables 1 and 2). The linear trend between HbA1c and the continuous variables was tested using linear regression adjusted for age and for categoric variables using chi-square test. To ensure a more symmetric distribution, fasting insulin was natural logarithmically transformed, and the geometric mean of fasting insulin was reported.

The hazard ratios for all-cause mortality were estimated using the Cox proportional hazard model for each cohort separately first, then for both cohorts combined. Adjustment was made first for age and center, and then additional adjustment for body mass index, systolic blood pressure, serum HDL-cholesterol, triglycerides, and smoking status. LDL-cholesterol and logarithmically transformed fasting insulin was fitted in the initial multivariate model but were not included in the final model because they did not significantly improve the model. To make the hazard ratios comparable between HbA1c, FPG, and 2-hr glucose, the hazard ratio for a one standard deviation increase, and for the upper 20% and middle 40% of the glycemic distributions compared with the lower 40% of the distributions were estimated. The three glycemic variables were estimated one by one in three separate models. Hazard ratios for combined categories of glycemic variables were also estimated. The interaction terms of center with glycemic variables and with all other confounding variables were modeled. The chi-square test statistic for measuring study-to-study variation in effect size was performed using a fixed-effects approach according to Fleiss [20]. The hypothesis of the test is that the two studies are homogeneous with respect to their effect sizes.

A chi-squared log-likelihood ratio test was used to test whether the predictive effect of HbA1c depended on 2-hr or fasting glucose levels and vice versa, modeling with continuous glycemic variables. SPSS for Windows 10.0 was used for statistic analysis.

3. Results

There were 156 deaths and 1,954 person-years accumulated in the Finnish cohort and 177 deaths and 9,051 person-years accumulated in the Hoorn cohort. The crude mortality rate (79.8/1,000 person-years) was higher in the elderly Finnish men than in the Dutch men (19.6/1,000 person-years), as expected from age. Mortality increased with increasing HbA1c levels (see Tables 1 and 2). The cutoff values for the quintiles of HbA1c were slightly higher in the elderly Finnish men than in the Dutch men. Mean 2-hr glucose concentrations were much higher in the elderly Finnish men than in the Dutch men in each HbA1c category, whereas mean FPG concentrations did not differ much between the two studies. Mean age was higher with increasing HbA1c levels in the Dutch men, but the increase was observed only for the highest quintile of the HbA1c in the elderly Finnish

Table 1
Baseline characteristics and mortality during the follow-up in subjects without a prior history of diabetes according to quintiles of HbA1c in Dutch men in the Hoorn study

	Quintiles of HbA1c distribution (%)					
	⩽5.0	5.1–5.2	5.3–5.5	5.6–5.7	⩾5.8	*P*-value
No. (%)	246 (22)	184 (17)	273 (25)	150 (14)	244 (22)	
Age (years)	59 (0.5)	60 (0.5)	62 (0.4)	62 (0.6)	63 (0.5)	<.001
HbA1c (%)	4.7 (0.03)	5.2 (0.03)	5.4 (0.03)	5.6 (0.04)	6.2 (0.03)	
Plasma glucose (mmol/L)						
Fasting	5.4 (0.07)	5.5 (0.08)	5.6 (0.06)	5.6 (0.08)	6.3 (0.07)	<.001
2-h	5.4 (0.18)	5.4 (0.21)	5.5 (0.17)	5.9 (0.23)	7.3 (0.18)	<.001
Fasting insulin (μU/L)[a]	77.4 (1.03)	79.0 (1.03)	77.7 (1.03)	82.4 (1.04)	80.6 (1.03)	.02
Body mass index (kg/m^2)	25.8 (0.2)	26.0 (0.2)	26.2 (0.2)	26.4 (0.2)	26.4 (0.2)	.001
Blood pressure (mmHg)						
Systolic	136 (1.2)	135 (1.4)	134 (1.1)	137 (1.5)	135 (1.2)	.64
Diastolic	84 (0.6)	84 (0.7)	83 (0.6)	83 (0.8)	83 (0.6)	.78
Cholesterol (mmol/L)	6.2 (0.07)	6.3 (0.08)	6.4 (0.07)	6.6 (0.09)	6.7 (0.07)	<.001
HDL-cholesterol (mmol/L)	1.2 (0.02)	1.3 (0.02)	1.2 (0.02)	1.2 (0.03)	1.1 (0.02)	<.001
LDL-cholesterol (mmol/L)	4.3 (0.07)	4.3 (0.08)	4.5 (0.06)	4.7 (0.08)	4.7 (0.07)	.05
Triglycerides (mmol/L)	1.5 (0.06)	1.5 (0.07)	1.5 (0.06)	1.7 (0.08)	2.1 (0.06)	<.001
Current smoking (%)	31.3	39.7	39.9	38.0	55.3	<.001
Follow-up (years)	8.2 (0.12)	8.2 (0.14)	8.4 (0.11)	8.3 (0.15)	8.1 (0.12)	.08
All-cause mortality, % (*n*)	9.3 (23)	12.5 (23)	13.9 (38)	20.7 (31)	25.4 (62)	<.001

Results are age-adjusted mean (standard error) except for noted.
[a] Geometric mean.

men. Mean cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol levels were higher with increasing HbA1c concentration in Dutch men. The mean systolic blood pressure was apparently higher for the elderly Finnish men than for Dutch men, but the mean diastolic blood pressure was not. More than half of the Dutch men in the highest quintile of the HbA1c concentration were smoking while this was only 15% in the Finnish men. Fasting insulin levels increased with increasing HbA1c in both cohorts. The Pearson's correlation coefficient between FPG and HbA1c was 0.60, between 2-hr glucose and HbA1c 0.49 and between FPG and 2-hr glucose 0.68. The chi-square test statistic for homogeneity was 0.11 for HbA1c, 0.50 for FPG, and 0.01 for 2-hr glucose, with *P*-values (1df) >0.10 for all. There was no statistical evidence rejecting the hypothesis that the two studies are homogeneous with respect to the effects sizes.

The hazard ratios for all three glycemic variables were significantly higher when only adjustment for age compared

Table 2
Baseline characteristics and mortality during the follow-up in subjects without a prior history of diabetes according to quintiles of HbA1c in Finnish men in the East and West Finland

	Quintiles of HbA1c distribution (%)					
	⩽5.0	5.1–5.3	5.4–5.5	5.6–6.1	⩾6.2	*P*-value
No. (%)	68 (21)	68 (21)	47 (15)	71 (23)	60 (19)	
Age (years)	76 (0.5)	76 (0.5)	76 (0.7)	76 (0.5)	77 (0.6)	.52
HbA1c (%)	4.8 (0.03)	5.2 (0.03)	5.5 (0.04)	5.8 (0.03)	6.6 (0.03)	
Plasma glucose (mmol/L)						
Fasting	5.5 (0.09)	5.5 (0.09)	5.7 (0.11)	5.9 (0.09)	6.2 (0.10)	<.001
2-hour	7.2 (0.32)	6.8 (0.32)	7.8 (0.38)	7.5 (0.31)	9.0 (0.34)	<.001
Fasting insulin (μU/L)[a]	51.9 (1.10)	50.7 (1.10)	61.3 (1.12)	56.1 (1.09)	71.7 (1.10)	.003
Body mass index (kg/m^2)	26.4 (0.5)	25.9 (0.5)	25.3 (0.5)	26.6 (0.4)	27.1 (0.5)	.06
Blood pressure (mmHg)						
Systolic	152 (2.7)	157 (2.7)	161 (3.2)	153 (2.6)	160 (2.8)	.29
Diastolic	82 (1.3)	84 (1.3)	84 (1.6)	83 (1.3)	88 (1.4)	.03
Cholesterol (mmol/L)	5.5 (0.13)	5.9 (0.13)	6.2 (0.16)	5.4 (0.13)	5.7 (0.14)	.73
HDL-cholesterol (mmol/L)	1.1 (0.04)	1.1 (0.04)	1.1 (0.05)	1.2 (0.04)	1.2 (0.04)	.17
LDL-cholesterol (mmol/L)	3.7 (0.12)	4.0 (0.12)	4.3 (0.14)	3.7 (0.12)	3.8 (0.13)	.80
Triglycerides (mmol/L)	1.4 (0.08)	1.5 (0.08)	1.6 (0.10)	1.3 (0.08)	1.5 (0.08)	.55
Current smoking (%)	10.3	19.1	17.0	11.3	15.0	.53
Follow-up (years)	6.4 (0.31)	6.4 (0.31)	6.2 (0.37)	6.1 (0.30)	6.0 (0.33)	.07
All-cause mortality, % (*n*)	42.6 (29)	50.0 (34)	53.2 (25)	50.7 (36)	53.3 (32)	.75

Results are age-adjusted mean (standard error) except for noted.
[a] Geometric mean.

with those with additional adjustment for other risk factors in Dutch men, but not in Finnish men (Fig. 1). Multivariate adjustment for other known risk factors studied did not reduce the hazard ratios in the elderly Finnish men. The multivariate adjusted hazard ratios for mortality did not significantly differ between the two cohorts, although it tended to be lower for fasting glucose in the elderly Finnish men (see Fig. 1). Mortality increased linearly with increasing 2-hr glucose, HbA1c, and fasting glucose concentrations, but the increase was significant only for the former two when data for the two cohorts were combined (see Fig. 1).

Men at the upper 20% of the 2-hr glucose distribution had a higher risk for death than men at the lower 80% of the distribution (Table 3). This did not change after adjustment for other risk factors studied and for HbA1c. Within each category of HbA1c, there was an increasing trend in hazard ratios with increasing 2-hr glucose levels, although it was statistically significant only in the lowest HbA1c category. Within each 2-hr glucose category, the hazard ratios increased also with increasing HbA1c levels, but the increasing trend was significant only in the lowest category of 2-hr glucose (see Table 3).

Compared with men with normal glycemia (2-hr glucose $<$7.8 mmol/L and FPG $<$7.0 mmol/L and HbA1c $\leqslant$6.5%), men who were impaired glucose tolerant or diabetic according to the 2-hr plasma glucose $\geqslant$7.8 mmol/L but nondiabetic according to FPG $<$7.0 mmol/L and HbA1c $\leqslant$6.5%, had a significantly increased risk of death (Fig. 2). In contrast, in men who were nondiabetic according to the 2-hr glucose $<$11.1 mmol/L but diabetic according to FPG $\geqslant$7.0 mmol/L and/or HbA1c $\geqslant$6.5%, the risk of death did not differ from men who were normal. Given the same FPG and HbA1c levels, the risk of death was 56% higher for men with 2-hr glucose $\geqslant$11.1 mmol/L and 35% higher for men with 2-hr glucose $\geqslant$7.8 mmol/L, compared with men whose 2-hr glucose was less than 11.1 mmol/L and less than 7.8 mmol/L, respectively. Men who had prior history of diabetes had the highest risk for death. Multivariate adjustment did not substantially change the observed risk of death.

Addition of the 2-hr glucose to the model based on both the fasting glucose and HbA1c significantly improved the prediction ($\chi^2 = 4.2$, 1*df*., $P < .05$), whereas neither HbA1c ($\chi^2 = 2.8$, 1 *df*., $P > .05$) nor fasting glucose ($\chi^2 = 1.2$, 1 *df*., $P > .10$) improved the prediction once the 2-hr glucose was in the model.

The interaction terms of center with glycemic variables or center with other variables were not significantly associated with the mortality, except a positive association for interaction of center with body mass index. But when the analysis was further stratified with centers, body mass index was not significantly associated with all-cause mortality in each of the two centers.

4. Discussion

Our data show that HbA1c and 2-h glucose concentration were predictors of all-cause mortality in Dutch and Finnish

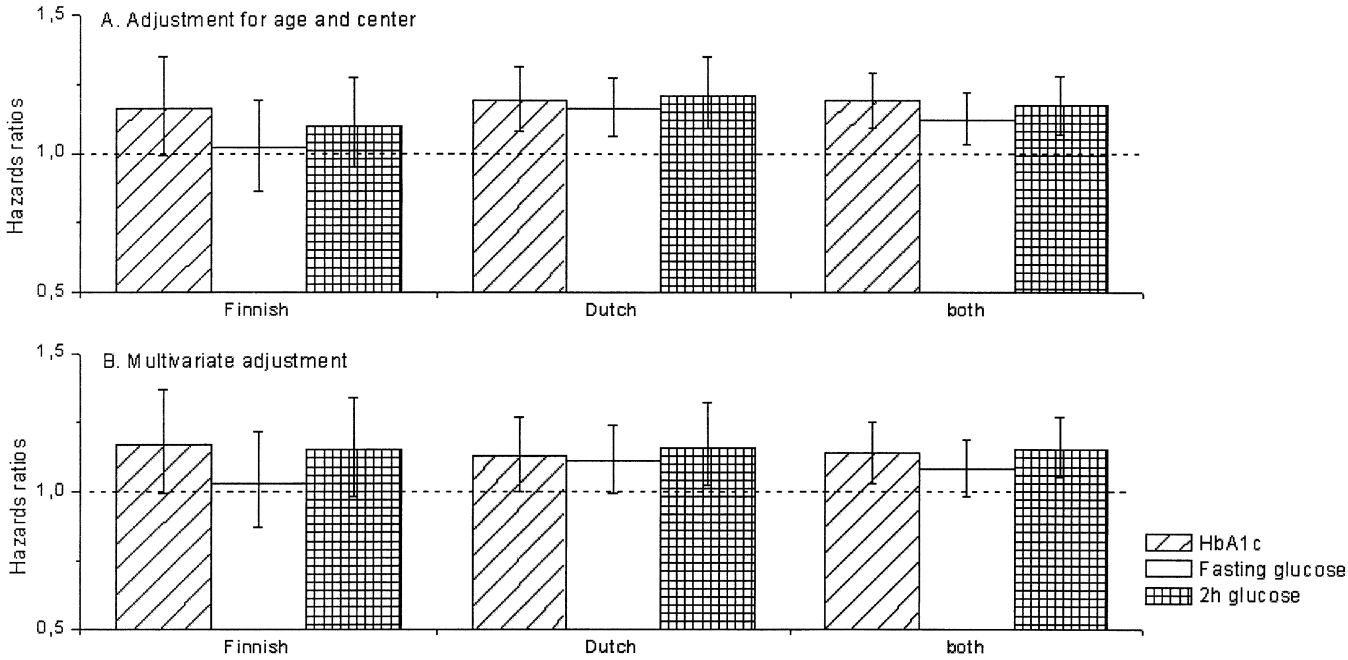

Fig. 1. Hazard ratios (column) and their 95% confidence intervals (vertical bar) for a one standard deviation increase in HbA1c (%, inclined line), in fasting (blank), and in 2-hr glucose (mmol/L, squared line) in men without prior history of diabetes, adjustment for age and cohorts if both studies combined (A), and additional adjustment for body mass index, systolic blood pressure, HDL-cholesterol, triglycerides and smoking (B). One standard deviation in Dutch (Finnish) men was 0.68% (0.66%) for HbA1c, 1.08 mmol/L (0.78 mmol/L) for fasting and 2.93 mmol/L (2.68 mmol/L) for 2-hr plasma glucose.

Table 3
Hazard ratios of all-cause mortality by HbA1c and 2-h or fasting glucose categories

	Percentiles of HbA1c (%)				
	<40th	40th–80th	≥80th	*P*-value for trend	All
Adjustment for age and center					
Percentiles of 2-h glucose (mmol/L)					
<40th	1	1.33 (0.87–2.03)	1.76 (1.06–2.92)	0.01	1
40th–80th	1.46 (0.97–2.20)	1.45 (0.96–2.17)	1.74 (1.09–2.78)	0.57	1.21 (0.94–1.56)
≥80th	1.47 (0.82–2.62)	1.81 (1.14–2.88)	2.09 (1.35–3.25)	0.26	1.48 (1.11–1.96)
P-value for trend	0.08	0.24	0.42		
Percentiles of fasting glucose (mmol/L)					
<40th	1	1.08 (0.73–1.61)	1.14 (0.67–1.95)	0.53	1
40th–80th	0.90 (0.60–1.36)	1.12 (0.76–1.63)	1.74 (1.15–2.61)	0.004	1.11 (0.87–1.42)
≥80th	1.25 (0.70–2.21)	1.47 (0.95–2.28)	1.46 (0.95–2.26)	0.70	1.35 (1.01–1.79)
P-value for trend	0.71	0.22	0.53		
All	1	1.19 (0.92–1.53)	1.50 (1.14–1.99)		
Multivariate adjustment[a]					
Percentiles of 2-h glucose (mmol/L)					
<40th	1	1.27 (0.83-1.94)	1.63 (0.98-2.71)	0.02	1
40th–80th	1.52 (1.00-2.30)	1.41 (0.93-2.12)	1.55 (0.97-2.50)	0.96	1.23 (0.95–1.59)
≥80th	1.50 (0.83-2.68)	1.90 (1.18-3.05)	1.86 (1.18-2.94)	0.55	1.49 (1.10–2.01)
P-value for trend	0.03	0.23	0.56		
Percentiles of fasting glucose (mmol/L)					
<40th	1	0.98 (0.65–1.47)	1.02 (0.60–1.75)	0.96	1
40th–80th	0.86 (0.57–1.30)	1.07 (0.73–1.56)	1.50 (0.99–2.27)	0.01	1.09 (0.85–1.40)
≥80th	1.21 (0.68–2.14)	1.45 (0.93–2.26)	1.23 (0.78–1.94)	0.86	1.30 (0.97–1.75)
All	1	1.14 (0.88–1.48)	1.33 (0.99–1.77)		
P-value for trend	0.98	0.29	0.32		

The lowest category of HbA1c and 2-h (fasting) glucose is used as reference group for HbA1c and 2-h (fasting) combined categories; the lowest category of HbA1c or 2-h or fasting glucose alone is used for "All" category.

The cutoff values of lower, middle, and higher categories of HbA1c for Dutch men (Finnish men) were <5.2 (5.3), 5.3–5.7 (5.4–6.1) and ≥5.8 (6.2); for 2-h glucose categories <4.9 (6.6), 5.0–7.0 (6.7–9.4) and ≥7.1 (9.5) and for fasting glucose categories <5.3 (5.4), 5.4–6.0 (5.5–6.2) and ≥6.1 (6.3).

[a] Adjusted for age, center, body mass index, systolic blood pressure, HDL-cholesterol, triglycerides, and smoking.

men. The association was independent of other established cardiovascular risk factors measured. The association of elevated HbA1c with high-mortality risk, however, partly depended statistically on the level of 2-hr glucose.

Population-based studies on the association of HbA1c with risk of death are rare. One prospective study showed that HbA1 (the sum of A1a, A1b, and A1c) is a better predictor of cardiovascular mortality than FPG or 2-hr glucose in women without diabetes, but not in men [9]. Subjects with newly diagnosed diabetes (2-hr glucose ≥11.1 mmol/L or FPG ≥7.8 mmol/L) were, however, not included in that study, and therefore the effect of postload hyperglycemia and the effect of fasting hyperglycemia on mortality were not evaluated simultaneously. Based on a prospective population study of 4,662 men aged 45–79 years, Khaw et al. [12] reported that HbA1c was continuously related to subsequent all-cause, cardiovascular, and ischemic heart disease mortality through the whole population distributions, with lowest rates in those with HbA1c concentration below 5%. In their study, fasting and 2-hr glucose were not taken into account either. In people at risk for diabetes, postchallenge glucose and glycemic excursions were found to be more strongly associated with carotid intima-media thickness than fasting glucose or HbA1c level [21]. Recently, the Framingham Offspring Study showed that postchallenge hyperglycemia is a risk factor for incident CVD, independent of fasting glucose and HbA1c levels, and the relation was stronger in elderly population than in young populations [11]. That 2-hr glucose was a better predictor for all-cause mortality than FPG or HbA1c in men and women combined in the Hoorn study has been reported previously, but the three-glycemic variables were not adjusted simultaneously [10]. In addition, because of the limit of the statistical power, further detailed analysis based on any of the single study cannot be made properly.

Glycated hemoglobin is an indirect measure of integrated glucose level over the previous 2–3 months [22]. The present observation, that part of the association of HbA1c with mortality risk is explained by 2-hr glucose, may reflect the contribution of postprandial glucose levels to individual HbA1c levels. The fitting with the three highly correlated glycemic measures in one model may, however, cause concern. Yet, if collinearity were the only explanation for the lack of independent effects of HbA1c or FPG when modeling together with 2-hr glucose, the risk with 2-hr glucose would also have been diminished in multivariate model. The fact that the 2-hr postload hyperglycemia remains a consistent independent risk predictor for all-cause mortality, regardless of model used, argues for a true independent effect.

Available evidence on the relationship between acute glycemic variations and diabetic complications was reviewed

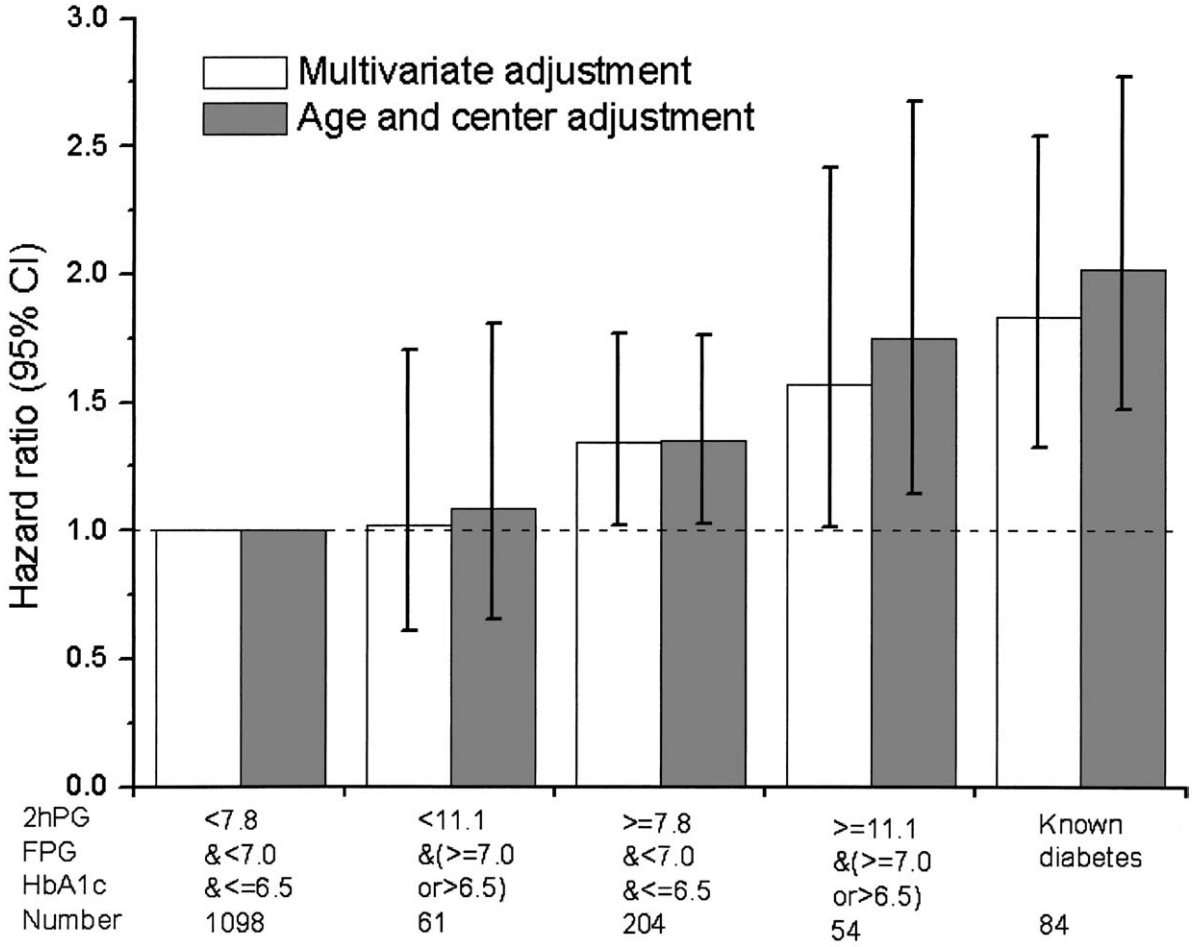

Fig. 2. Hazard ratios (column) and their 95% confidence intervals (vertical bar) for combined glycemic categories and for previous diagnosed diabetes, adjustment for age, cohorts, and additional adjustment for body mass index, systolic blood pressure, HDL-cholesterol, triglycerides, and smoking.

recently by Ceriello [23]. The author concluded that acute increases in blood glucose level after a meal appear to be harmful, and can induce alterations of homeostasis in healthy subjects, and even in diabetic subjects whose baseline plasma glucose is in the hyperglycemic range [23]. The mechanisms through which acute hyperglycemia exert its effects may be identified in labile nonenzymatic glycation, promotion of thrombosis, and in production of free radicals. Alternatively, the effect of 2-hr glucose may reflect other metabolic disturbances, like dyslipidemia, insulin resistance, hypertension, and abdominal obesity because glucose intolerance often appears together with these risk factors [24,25]. However, multivariate adjustment of the risk factors including fasting insulin, a surrogate indicator for insulin resistance, did not significantly change the results. However, abdominal obesity as well other factors that were not measured were not adjusted for and the confounding effect of the unmeasured factors could not be estimated, and need to be further studied. More recently, Ceriello et al. [26] showed an independent and cumulative deleterious effect of both postprandial hypertriglyceridemia and postload hyperglycemia on endothelial function in both type 2 diabetic patients and in healthy controls, and suggested that oxidative stress is the common mediator through which they exert such an effect.

Although there is growing epidemiologic evidence showing that postload hyperglycemia is an important risk factor for future morbidity or mortality [1–7,27], the clinical trials, so far, have not been designed to study the benefit of lowering specifically the postload blood glucose levels. The landmark trial in this area, the UK Prospective Diabetes Study (UKPDS) [28], did not find convincing evidence supporting the hypothesis that lowering fasting blood glucose concentration by intensive treatment with sulphonylurea or insulin can reduce the risk of all-cause mortality. But in the UKPDS, postload glucose excursion, was not available, and over 10 years, the difference in Hba1c concentration between intensive and conventional groups was only 0.9% (7.0 vs. 7.9%).

There are different techniques for the measurement of HbA1c. Even techniques that use the same analytical method often report dissimilar values because of both the lack of standardisation in HbA1c measurement and the variability in performance between instruments [29]. In this study, the high-performance liquid chromatograph method (HPLC) was used for measurement of HbA1c in both centres, which

reduced the variation that may be related to analytic methods. However, we did not standardize the measurement of HbA1c. The lack of standardisation would not affect the association observed between HbA1c and mortality because a stratified analysis based on each individual study was applied, and the center was used as a covariate in the pooled analysis.

We conclude that elevated 2-hr glucose was a risk predictor of all-cause mortality, independent of the levels of fasting glucose and HbA1c in Dutch and Finnish men aged 50–89 years.

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